

What can the pathologist offer for optimal treatment choice?

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The choice of the most appropriate systemic treatment of patients with metastatic breast carcinoma is a multifaceted decision-making process. The role for the pathologist is to provide a definite diagnosis of metastatic breast carcinoma, whenever needed, and especially to assess the biological parameters with prognostic and predictive value. Although the vast majority of breast carcinomas maintain the same biological features both in the primary and in the metastases, some undergo changes that may indicate that a targeted systemic treatment should be stopped or started, be it endocrine or anti-HER2. Unfortunately these tumours cannot be easily identified clinically, and it may be useful to biopsy the metastatic sites for reassessment of the biological characteristic of the tumours. Intra-tumoural heterogeneity and clonal selection due to the therapy could explain changes in biological features during tumour progression, but it should also be taken into account that the available assays for evaluating hormone receptor and HER2 status are not 100% accurate, even in the hands of expert pathologists. To minimize the risk of inducing inappropriate changes in systemic treatments due to false-positive or false-negative results, the pathologists should make all efforts to improve accuracy and reproducibility of the assay procedures.

Key words: oestrogen receptors, HER2, immunohistochemistry, in situ hybridization, metastatic breast cancer

introduction

The selection of the most appropriate systemic treatment of patients with metastatic breast carcinoma is guided by a combination of disease- and patient-related factors. These include the hormone receptor (HR) and HER2 status of the primary tumour or its metastases, the length of disease-free interval since surgery and since completion of adjuvant treatments, the effects and tolerance of previous therapies, the number and sites of metastatic lesions, the age, menopausal status, comorbidities and performance status of the patient, the availability and access to treatments and patient preference [1–3].

In this multifaceted decision-making process, the pathologist may be required to confirm that the lesions actually are metastases from the primary breast cancer, and to characterize the biological features of the metastatic tumour by reassessing HR and HER2 status.

diagnosis of metastatic breast cancer

Despite the consensus that histological or cytological confirmation of metastatic disease is not required routinely [3], a biopsy of the metastatic lesion may be advisable in case of ambiguity. Fine-needle aspiration cytology (FNAC) may be a reasonable approach for accessible metastatic sites, with minimal morbidity for the patients. FNAC is a very accurate

diagnostic tool for metastatic disease, with a negligible false-positive rate, and a false-negative rate strictly dependent on the sampling procedure. Cytological preparations of metastatic tumour are suitable for the assessment of HR status by immunocytochemical assays, whereas HER2 status has to be evaluated using in situ hybridization assays with either fluorescent (FISH) or chromogenic (CISH or SISH) probes. When carrying out FNAC for a suspected metastasis of breast carcinoma, it is necessary to foresee the need for the biological characterization of the neoplastic cells. This implies that the lesion has to be extensively sampled, and multiple cytological preparations obtained to allow for complete characterization of the disease.

Biopsies of the suspected lesions allow better characterization of the morphological and biological features of the tumours. Not infrequently, a biopsy of a suspected metastasis from breast cancer shows non-neoplastic disease, or a different tumour, either a second primary or a metastasis from an unsuspected non-mammary primary. Examples include suspected breast metastases to the lung revealed to be primary lung tumours, or liver metastases thought to originate from breast cancer, but actually representing either metastatic neuroendocrine tumours from the gastrointestinal tract, or metastases from tumours of different origin. It is therefore essential that the pathologist examining a suspected breast metastasis always thinks of the possibility of a different tumour, especially when the neoplastic cells exhibit a negative HR status. In this case, the morphological features of the tumour may not be sufficient to confirm or exclude the breast origin, and it is advisable to carry

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out immunohistochemical assays for the identification of markers indicating an alternative possible origin of the metastatic disease (e.g. GCFDP-15 for the breast, TTF-1 for the lung, CDX2 for the gastrointestinal tract, etc.).

assessment of the biological features

It is still debated whether the reassessment of the biological features (HR and HER2 status) of metastatic breast cancer per se justifies a biopsy of the metastatic site, whenever this is feasible. There may be two different scenarios. In the unlikely event that the HR and HER2 status of the primary tumour is not known, this information undoubtedly has to be collected, either by retrieving and examining the original tumour samples, or by carrying out a biopsy of the metastasis.

If the biological features of the primary tumour are known, the question arises of whether it is worth reassessing HR and HER2 status of the metastasis. Those who advise reassessment of the biological features of the metastases whenever feasible support their recommendation by emphasizing that breast tumours have been repeatedly reported to potentially undergo changes of their biological characteristics during tumour progression. Indeed, several studies in the last decades have documented changes in HR and HER2 status of some 10%–20% of the metastases as compared with the breast primary [4–10]. As a matter of fact, however, the vast majority of metastases maintain the biological features of the primary tumours, and we cannot easily identify those tumours most likely to undergo changes (and therefore worth being biopsied at the metastatic site). Some hints that a tumour may have changed its biological features may be derived from the clinical course of the disease, and the response to systemic treatments. If the time to recurrence or the site of recurrence appear to be different from what is expected according to the features of the primary tumour, then reassessing HR and HER2 status in the metastasis is very important for optimal treatment choice.

The changes in the biological features of the metastatic tumours mandate stopping or starting a targeted systemic treatment, be it endocrine or anti-HER2. Patients who no longer have HR-positive cancers at the time of recurrence are unlikely to benefit from further endocrine therapy. On the other hand, tumours that acquire estrogen receptor (ER) or HER2 expression might become responsive to endocrine or HER2-targeted therapies. The most commonly accepted biological explanations for change in receptor status are tumour heterogeneity with a possible clonal selection due to therapy, and divergent differentiation of breast tumorigenic cells during the course of the disease [11]. Discordance for ER, progesterone receptor and HER2 was encountered in 18.4%, 40.3% and 13.6%, respectively, of 789 patients with recurrent breast cancer in a recent study [12]. Patients with concordant receptor-positive breast cancer had significantly better post-recurrence survival than discordant cases; patients with discordant receptor status had an unfavourable survival as did patients with concordant triple-negative disease. The poor survival of patients with tumours exhibiting changes in receptor status was probably due to inappropriate use of targeted therapies.

The importance of an accurate assessment of the predictive parameter cannot be overemphasized. Unfortunately, however, we have to admit that the currently available assays (immunohistochemistry and in situ hybridization) are not 100% accurate and reproducible, even in the hands of experienced pathologists. Therefore, when using an assay that has a 5% error rate (implying that it has a remarkable accuracy of 95%) to test the primary tumour and thereafter the metastatic tumour, the risk of a different assessment of the biological parameter under study is ~10%. If the error rate of the assay is higher, then the risk of apparent changes in the biological features of the tumours increases dramatically, and it becomes almost impossible to ascertain whether the tumour has actually changed during progression or if the changes reflect the imperfect accuracy of the testing procedures. The diagnostic problem is that considering the two separate test results alone, one cannot determine whether the first or second biopsy result was correct for these discordant cases.

To try and minimize the possibility of a false assessment of changes in the biology of the tumour, and hence in the expected response to the therapeutic approaches, the pathologist has to double-check the reliability of the results before reporting any change in the HR and HER2 status of the metastatic tumours. To do this, it is advisable to repeat the assays for the biological variables that are discordant in the primary and metastatic samples on both lesions simultaneously in the same testing conditions. This will reduce the chance of errors due to the analytical procedures. Another useful suggestion would be to add a confirmatory test (e.g. a FISH assay for HER2 in the case of discordant immunohistochemical results or vice versa) before rendering the final diagnosis. Though this policy will not completely eliminate false-positive and false-negative results, in the experience of the authors it has been proved to remarkably reduce the ER and HER2 discordance rate between primary and recurrent tumours. If this may avoid an inappropriate change in systemic treatment of some patients it is well worth the additional effort and costs afforded by the pathologists.

disclosure

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